Title:

The default mode network mediates the impact of infant regulatory problems on adult avoidant personality traits

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Abstract:

Background: Infant regulatory problems (RPs), i.e. problems with crying, feeding, and/or sleeping, are associated with behavioral and emotional problems in childhood. It is unclear, however, whether these behavioral and emotional problems persist into adulthood. The default mode (DMN) and salience networks (SN) support both interoceptive regulation and social/emotional abilities. We thus hypothesized that adults with infant RPs have more behavioral and emotional problems, mediated by DMN/SN alterations.

Methods: Within the scope of the Bavarian Longitudinal Study, adults (mean age 28 years; 50% females) with (N = 79) and without (N = 254) a history of multiple and/or persistent infant RPs were assessed by the Young Adult Self Report (YASR) to measure behavioral and emotional problems, and – in a sub-sample (N = 49 and N = 71) – by resting-state functional magnetic resonance imaging (rs-fMRI) to measure DMN/SN integrity via intrinsic functional connectivity (iFC).

Results: Compared to adults without infant RPs, adults with infant RPs had more total problems (p=0.002), internalizing problems (p = 0.005), and more avoidant personality traits ($p < 0.001$). They showed decreased iFC of the DMN and SN. DMN iFC-decreases were strongest in adults with multiple *and* persistent RPs and linked with avoidant personality traits (r = - 0.42, p = 0.006). Remarkably, DMN iFC-decrements fully mediated the association between infant RPs and adult avoidant personality traits.

Conclusions: Adults with infant RPs have more avoidant personality traits that are mediated by the DMN. Persistent/multiple infant RPs and the DMN may be targets to attenuate behavioral and emotional problems.

Introduction

Infant crying is a normal part of neurobehavioral development with the majority of infants following a similar crying pattern(1). However, in some infants crying duration exceeds the normal duration for a given age (e.g. ≥ 2 hours per day beyond the age of three months), with the causes being elusive, i.e. not explained by circumscribed organic diseases(2, 3). Often, excessive crying is accompanied by additional problems in sleeping and feeding (e.g. infant wakes up ≥ 2 times per night, infant does not eat and drink well(4)). Together, these symptoms have been subsumed under the term 'infant regulatory problems'(4-6). RPs are relatively common in young infants. For example, single problems (e.g. excessive crying) occur in up to 45% of infants in their first year of life(6). In contrast, multiple infant RPs (e.g. excessive crying and sleeping problems) are less frequent with a prevalence of 2 to 20%(4, 7-9). While RPs are transient for the majority of affected infants(10), in a considerable number of infants (~8%) they are stable across the preschool years(11) and a major concern for affected parents and healthcare providers.

While initial symptoms (e.g. excessive crying) cease as the child gets older, many infants with RPs go on to develop behavioral and emotional problems by late childhood, particularly if RPs were present in multiple and/or persistent forms(6). For instance, several studies indicated that children with infant RPs are at an increased risk of developing deficits in social skills(11), internalizing and externalizing problems, and Attention-Deficit/Hyperactivity Disorder (ADHD)(6, 12). It is unclear, however, whether RPs-related behavioral and emotional problems persist into early adulthood. Comparable findings in congeneric samples (e.g. behaviorally inhibited children or children with conduct problems) suggest lasting behavioral and emotional problems, likely persisting into early adulthood(13, 14). Furthermore, theoretical accounts on emotion development emphasize the role of social regulation of basic physiological needs and emotions (e.g. by primary caregivers) for the successful development of regulatory capabilities in infants(15-17). These models suggest that early problems with the regulation of basic

physiological needs and emotions may have long-term effects on behavioral and emotional development(10). Based on these findings, we hypothesized that individuals with a history of infant RPs have more behavioral and emotional problems in adulthood, as measured with the Young Adult Self Report (YASR)(18), than individuals without infant RPs (hypothesis 1). Information about the persistency of such problems is important as behavioral and emotional problems – both in the clinical and subclinical range – are hallmarks of and risk factors for several psychiatric disorders, such as affective disorders, social anxiety disorder, and schizophrenia(19-21). Furthermore, if infant RPs are indeed associated with increased adult behavioral and emotional problems, then the identification of brain mechanisms contributing to such problems would be essential to develop specific prevention and intervention strategies. A method to investigate such brain mechanisms at the large-scale brain level is resting-state functional magnetic resonance imaging (rs-fMRI); rs-fMRI allows to quantify the temporal coherence of ongoing (i.e. intrinsic) blood oxygenation level dependent (BOLD) fluctuations across spatially distinct brain areas. Brain areas whose BOLD-signals fluctuate synchronously show a high intrinsic functional connectivity (iFC). Such iFC-patterns reflect a basic organizational principle of large-scale brain activity, namely the organization into distinct intrinsic brain networks(22). Accordingly, the present study tested the hypothesis that alterations in the iFC of two intrinsic brain networks, the default mode (DMN) and salience networks (SN), would mediate the effect of infant RPs on adult behavioral and emotional problems (hypothesis 2).

To understand the specific outline of this second hypothesis, one should recall the following. First, DMN and SN are domain-general intrinsic networks involved in a wide range of psychological functions such as prospection, memory, theory of mind, empathy, and emotions, to name a few(23-26) (for review see(27-29)). However, both the DMN and SN appear to be particularly relevant for the interactions of the individual with its social environment(28, 30). For instance, a recent meta-analysis demonstrated the DMN and SN to strikingly overlap with

two brain networks constituting the neural underpinnings of social cognition and emotional processing, respectively(31). Accordingly, aberrant functioning of DMN and SN is accompanied by deficits in social cognition, social interaction, and emotional processing, as evident in several psychiatric disorders such as autism spectrum disorder(32-34), schizophrenia(35, 36), as well as major depression(37, 38). As similar deficits - yet to a lesser degree - have been observed in children with infant RPs(6), we expected DMN/SN alterations being linked with behavioral and emotional problems in adults with infant RPs.

Secondly, DMN and SN are part of a larger allostatic-interoceptive system(39). Previous studies suggest that this system continually anticipates the body's energy needs with the goal of meeting those needs before they arise (e.g. food intake before the blood sugar gets too low). This process is called allostasis(40). Allostasis ensures the availability of resources necessary for an organism to grow, survive, thrive and reproduce. Likewise, all psychological functions performed in the service of growing, surviving, thriving and reproducing (e.g. social interactions) require the efficient regulation of biological resources(39). This circumstance may explain why the very same brain system (consisting of DMN and SN) subserves both basic regulatory processes (i.e. predictively regulating the body's physiology) and a wide range of psychological functions(39). As the allostatic-interoceptive system prepares the organism for current and upcoming interactions with the social and physical environment (see also(41-43)), allostatic-interoceptive regulatory processes are essential for any behavioral function, but particularly for social/emotional functions(44). Thus, allostatic-interoceptive functions are not distinct, but equivalent to social and emotional functions. Some authors have even argued that social stimuli are inherently linked to allostasis because they help organisms to regulate their needs. This is particularly the case for human infants, who require caregivers to regulate their allostasis for many years of their lives(15). Based on this evidence, we suggest that alterations in the allostatic-interoceptive system, namely DMN and SN, do mediate the effect of infant RPs on adult behavioral and emotional problems.

Materials and methods

Study design, participants and measures

The BLS is a geographically defined whole population sample of neonatal at-risk children born between January 1985 and March 1986 in Southern Bavaria (Germany)(45). The present prospective case-control study utilizes data collected from birth to early adulthood. Out of 1495 participants invited for the 6-year assessment, we excluded those who had single and transient RPs or missing data on crying, sleeping or feeding problems at any assessment from 5 to 56 months (Figure 1). Of the eligible 708 participants, we were able to follow up 342 adults of whom 333 completed the YASR, main outcome of the current study. Participants from this sample were subsequently invited to take part in the rs-fMRI study. Before entering the imaging study, each participant was carefully screened for MR-related contraindications (e.g. claustrophobia, pregnancy, ferromagnetic implants). Finally, 49 adults with and 73 without infant RPs were willing and able to participate in the MRI sub-study. Groups (never RPs vs. multiple and/or persistent RPs) were matched for potential confounding variables, such as gestational age, sex, socioeconomic status, as well as scanner type (for variable definitions see supplemental materials; for final group characteristics see Table 1). Ethical approval for the study was granted by the ethics committees of the University of Munich Children's Hospital, the Bavarian Health Council (Landesärztekammer Bayern), and the University Hospital Bonn. Informed consent was obtained from parents (childhood) and participants (adulthood).

RPs.

As part of a neurodevelopmental assessment, pediatricians conducted a standardized interview with the parents concerning their child's crying, feeding and sleeping problems at 5 months. At 20 and 56 months, sleeping and eating problems were assessed via standardized parental interviews, while the neurological examination of oral motor function was conducted by pediatricians. The detailed definitions for crying, feeding and sleeping problems at 5 months

and sleeping and eating problems at 20 and 56 months can be found in Table S1 and in(11). The assessments at 5 and 20 months were carried out corrected for premature birth and the 56 months' assessment at chronological age (Table 1). RPs were categorized as single (e.g. single crying problem) or multiple (e.g. crying and sleeping problems), and transient (RPs present at one or two measurement points) or persistent (RPs present at all three measurement points).

Behavioral and emotional problems.

To assess behavioral and emotional problems in adulthood, we used the German version of the YASR, which includes 119 questions of distinct types to evaluate multiple traits and problems(18). General behavioral and emotional problems were assessed with the Sum-scales, covering internalizing, externalizing and total problems. The Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition (DSM-IV)-oriented scales (Depressive, Anxiety, Somatic, Avoidant personality, Attention deficit/hyperactivity problems, and Antisocial personality) were used to evaluate which aspects of behavioral and emotional functioning were impaired (Table 2). As the DSM-oriented scales overlap to a large degree with the syndrome scales, the latter are not reported here(18). We used T scores of the scales as outcome measures.

MRI.

As our rs-fMRI account on social-DMN iFC follows canonical procedures, their current description is brief (for more details see supplemental materials and elsewhere(46)).

MRI data acquisition and preprocessing. MRI data were acquired by gradient-echo echo-planar sequences at two sites, Klinikum rechts der Isar der Technischen Universität München and University Hospital Bonn (for sequence specifications please refer to the supplemental materials). To account for the effect of different scanners, participants of both groups were equally distributed across all four scanners ($\chi^2(3) = 1.39$, $p = 0.708$). In addition, data analyses included scanner types as dummy control variables. Rs-fMRI data were preprocessed using

FSL(47), including realignment, non-brain-tissue removal, spatial smoothing with a Gaussian kernel of FWHM 5 mm, high-pass temporal filtering (200s), co-registration to structural T1-image(48), and normalization to MNI space at 2 x 2 x 2-mm resolution(49). Four RPs- and two non-RPs subjects had to be excluded due to excessive head motion, defined as a cumulative motion translation or rotation > 3 mm or 3° and mean point-to-point translation or rotation > 0.15 mm or 0.1°. Three RPs subjects were excluded due to missing/incomplete resting-state scans. The final imaging sample consisted of 42 adults with and 71 without infant RPs. Both groups did not differ in head motion parameters, namely point-to-point translation or rotation of any direction ($p = 0.18$) and frame-wise displacement ($p = 0.18$)(50, 51).

Brain outcome measure – iFC of the DMN and SN.

To investigate the iFC of the DMN and SN, we used the following multi-step procedure. Cortical rs-fMRI activity was separated in distinct intrinsic brain networks by independent component analysis (see networks in Figure S1). Networks of interest were chosen based on their spatial correlation with the meta-analytically defined maps of social cognition and emotional processing, respectively(31). To foreshadow results, the posterior DMN (cf.(52)) most strongly correlated with the social cognition-, and the SN with the emotional processing network. Non-overlapping cortical component masks were created by assigning each voxel to one specific component depending on which component had the highest Z-score at that voxel(53). Via dual regression and group cortical network masks, subject-specific spatial networks were defined(54), and used to define network-specific time courses. These time courses were ultimately entered into single partial correlation models to calculate the (partial) correlation between the time course of the posterior DMN and SN, respectively, and the time series of each other voxel in the brain, regressing out the time series of all other networks, the signal of white matter and cerebrospinal fluid, as well as the six head motion parameters. The partial correlation approach helped to identify those voxels in the brain which were specifically

correlated with one specific network and not the other. Finally, resulting partial r-maps per subject were converted into Z-maps using Fisher's r-to-z transformation.

To assure that effects of infant RPs on intrinsic networks were specific to DMN and SN, the very same procedure was repeated for the sensorimotor network (SMN). The SMN was chosen as control network as there is no evidence for the SMN's involvement in either behavior or interoceptive processes and thus no RPs-related effects were expected.

Statistical analyses

Between-group differences: Group differences in the YASR were tested by Mann-Whitney U-Tests, as implemented in SPSS (significance threshold $p < 0.006$, Bonferroni adjusted for multiple testing). Behavioral problems in the clinically relevant range (T-value >= 64) were tested by Chi-square tests. In the MRI sub-sample, we restricted our analyses to those YASR scales that showed significant (i.e. Bonferroni adjusted) group differences in the whole sample. To test for group differences in DMN, SN and SMN between adults with and without infant RPs, we used voxel-wise two-sample t-tests as implemented in SPM 8, controlling for gestational age, sex and scanner type ($P < 0.05$, FWE corrected). Group differences in DMN and SN were overlapped with the meta-analytically derived social cognition and emotional processing maps, respectively, defined by Schilbach and colleagues(31).

Within-group differences: To test which aspect of RPs (i.e. single-persistent, multiple-transient, multiple-persistent RPs) was most strongly associated with changes in DMN/SN iFC, we performed one-way ANCOVAs with three levels and subsequent post-hoc t-tests within the RPs-group, controlling for gestational age, sex and scanner type.

Brain-behavior relationship and mediation analysis: To test whether variance in DMN/SN iFC was associated with behavioral and emotional problems, averaged group-different iFC (controlled for scanner type) was correlated with group different YASR T-scores via Spearman's rank correlation. To test whether DMN iFC (controlled for scanner type) mediated

the association between infant RPs and adult avoidant personality trait, mediation analysis was performed. Path coefficients were estimated using (unstandardized) regression coefficients of multiple regression analyses, and statistical significance of the indirect effect was tested using a nonparametric bootstrap approach (with 5000 repetitions) to obtain 95% confidence intervals using the SPSS PROCESS Macro(55).

Results

Adults with infant RPs have more behavioral and emotional problems than adults without RPs

Adults who had infant RPs were more likely to have total problems (p=0.002), internalizing problems in the subclinical (p = 0.005) and clinical range (p = 0.021), and more avoidant personality traits (p < 0.001) in comparison to the ones who never had RPs (Table 2). They were also more likely to have externalizing problems (p = 0.014), somatic complaints (p = 0.010) and ADHD problems (p = 0.036), as well as anti-social personality traits (p = 0.011) when compared to the ones who never had RPs. Nevertheless, the differences in the latter scales disappeared after correction for multiple testing (p < 0.006, Bonferroni adjusted).

Adults with infant RPs show decreased iFC of the DMN and SN

Concerning the MRI sub-sample, adults who had infant RPs were more likely to have avoidant personality traits in comparison to the ones who never had RPs (p = 0.037). There were, however, no group differences in internalizing or total problems (p > 0.05). Voxel-wise two-sample t-tests revealed that adults with infant RPs had a significantly decreased DMN iFC in the precuneus and medial prefrontal cortex, as well as decreased SN iFC in lateral occipital cortices (p < 0.05, FWE-corrected). DMN iFC overlapped with the social cognition network, while SN iFC differences showed little overlap with the emotional processing network (Figure 2 B1, B2; Table S2a,b). Mean iFC of the DMN clusters differed significantly across RPs sub-groups ($F(2, 38) = 4.43$, $p = 0.019$), with strongest decreases in adults with multiple *and* persistent RPs (Scheffe's post-hoc test, p = 0.04) (Figure 2 C1). SN iFC did not show similar effects of infant RPs ($F(2, 38) = 1.02$, $p = 0.37$). IFC in the SMN was not different between adults with and without infant RPs, indicating the specificity of our results for the DMN and SN.

Decreased DMN iFC is related to avoidant personality traits in adults with infant RPs

Decreased residual iFC in the posterior DMN was associated with an increase in avoidant personality traits ($r = -0.42$, $p = 0.006$) (Figure 2 D1). This association was not significant in adults who never had infant RPs ($r = -0.01$, $p = 0.92$). Across all subjects, the correlation between residual posterior DMN iFC and avoidant personality traits was $r = -0.22$, $p = 0.02$. In contrast, group-different residual SN iFC was not significantly related to avoidant personality traits, neither within the RPs-group ($r = 0.12$, $p = 0.44$), nor across all participants ($r = -0.02$, $p = 0.85$).

DMN iFC fully mediates the relation between infant RPs and adult avoidant personality traits

In the mediation analysis (Figure 3), the association between infant RPs and adult avoidant personality traits (total effect: $c = 2.07 \pm 1.27$), was not significant when controlling for residual posterior-DMN iFC (direct effect: $c' = 0.54 \pm 1.40$). Moreover, the bootstrapped confidence interval revealed the indirect effects (i.e. the mediation: total – direct effect) to be significantly different from zero (0.52, 3.22).

Discussion

Adults with a history of infant RPs had more total behavioral and emotional problems, in particular more internalizing problems, both in the clinical and subclinical range, as well as more avoidant personality traits than adults without infant RPs. This finding indicates that multiple and/or persistent infant RPs have long-term effects on behavioral and emotional functioning in adulthood. It contradicts a previous study,(56) which demonstrated a significant association between infant RPs and behavioral and emotional problems in childhood, but not in adolescence and early adulthood. However, Hyde et al. did not distinguish between transient and persistent RPs. Moreover, they assessed RPs only once (at six months of age) instead of several time points (i.e. at 5, 20, and 56 months of age) as in the present study. Thus, their study does not allow to make a distinction between single/multiple and transient/persistent RPs. Assessment of multiple/persistent RPs may provide long-lasting impacts since it was shown that only multiple and/or persistent RPs affect the child's behavior, while transient RPs show an overall good prognosis(12, 57, 58). Except for internalizing problems, aberrant YASR scores were in the subclinical range, indicating mild to moderate lasting effects of infant RPs on adult behavior. However, it should be noted that such mild to moderate problems represent relevant risk factors for later psychiatric disorders, such as major depression and anxiety disorders,(59) as well as life outcomes, such as work and social relationships(60, 61). As most participants were young adults (mean age: 28 years) at the time the study was conducted, one cannot rule out the possibility that subclinical behavioral problems turn into more severe forms later in life(19).

Interestingly, infant RPs mainly predicted adult behavioral and emotional problems within the internalizing spectrum. This is in contrast to childhood data where externalizing problems and ADHD were the predominant behavioral and emotional problems(6). Even though significant associations between infant RPs and both externalizing problems and ADHD in adulthood were

found in the current study, these associations disappeared after correcting for multiple comparisons. This may be due to the lack of statistical power with a relatively small sample size. In addition, two other explanations may also be able to account for these results. First, externalizing problems mitigate in a remarkable portion of children as they get older(62, 63). Secondly, internalizing problems in childhood may comprise a "secret illness"(64) as they are often difficult to detect by external observers. This may result in a systematic over-representation of externalizing problems and an under-representation of internalizing problems in childhood data.

The DMN mediates the association between infant RPs and adult avoidant personality traits

Adults with infant RPs showed decreased iFC of the DMN in the precuneus and medial prefrontal cortex, as well as of the SN in lateral occipital cortices (Figure 2 B1). In contrast, SMN iFC was unchanged in the RPs group, indicating that RPs-related iFC alterations do not influence all intrinsic networks in the same manner. The impact of infant RPs on adult DMN iFC was strongest in adults with multiple *and* persistent RPs, suggesting DMN iFC decrements to follow a 'dose' response (Figure 2 C1). This dose effect was absent in SN iFC indicating SN alterations to not follow a similar trajectory.

Interestingly, DMN iFC group differences showed a marked spatial pattern strikingly overlapping with the social cognition network (Figure 2 B1). In contrast, iFC differences in the SN showed little overlap with the emotional processing network(31). The social cognition network refers to the meta-analytically defined neural correlate of social cognition(31). Thus, aberrant iFC of the DMN – overlapping with the social cognition network – may reflect impaired social cognition and associated changes in social behavior, such as social withdrawal. Moreover, the pattern and direction of DMN iFC changes resemble findings in several psychiatric disorders, such as major depression(65), ADHD(66), autism(32-34), as well as

schizophrenia(35, 36). Although most adults with infant RPs in the present study did not receive psychiatric diagnoses per se, they showed more social withdrawal/avoidant behaviors (Table 2), which are core symptoms of aforementioned psychiatric disorders(67). Thus, decreased DMN iFC may be the neural underpinning of a socially withdrawn phenotype independent of the etiology. For instance, a study investigating DMN iFC alterations in adolescents and young adults with autistic spectrum disorder – a disorder characterized by social withdrawal behavior and deficits in social cognition – found an inverse correlation between decreased precuneus/medial prefrontal cortex iFC and the severity of patients' social and communication deficits(33). In line with that, we found RPs-related avoidant personality traits to be correlated with DMN iFC decreases, i.e. the more DMN iFC was decreased, the more were avoidant personality traits pronounced (Figure 2 D1). Even more, DMN iFC alterations fully mediated the effect of infant RPs on adult avoidant personality traits. This finding suggests DMN malfunctioning to be an important factor in contributing to RPs-related social withdrawal/avoidant problems. In contrast, avoidant personality traits showed no correlation with decreased SN iFC, possibly due to the lacking overlap with the emotional processing network(31).

A possible explanation for the intimate link between body-oriented regulatory problems, DMN alterations, and avoidant personality traits may reside in the DMN's role in the allostatic-interoceptive system. The allostatic-interoceptive system constantly matches the body's current physiological processes to its behavioral state(39). Aberrant functioning of the DMN may thus result in a mismatch between the body's signals and the brain's interpretation and prediction of those signals in the interactions with the (social) environment, ultimately giving rise to mental disorders and associated symptoms(42, 68). For instance, withdrawal behavior has often been linked to social fear and associated sensations of intense physiological arousal(67). Thus, social withdrawal may be a coping mechanism of affected individuals to reduce visceral arousal(67).

As the DMN plays a vital role in the regulation and representation of such visceral-interoceptive processes, DMN alterations may have an important mediating role in this matter.

Further issues: implications, strengths, and limitations

In the following sections we briefly list both potential implications of our findings for individuals with infant RPs and the study's potential strengths and limitations.

Implications. The DMN mediates the link between infant RPs and adult avoidant personality traits as well as the link between social cognition/interactions and emotion regulation. For example, we recently demonstrated that socially-induced emotion regulation (i.e. in which a social 'interactant' regulates another 'target' person's emotions via, for example, reappraisal) works by 'activating' the target person's DMN(69). These 'parallel' findings have important implications:

(i) *For the origin of infant RPs:* if socially-induced emotion regulation in adults depends on the DMN, then analogously, impaired body-focused regulation in a RPs-social caregiver context, may depend on congenital DMN impairments and/or deficits in the interactions with primary caregivers(15).

(ii) *For development of RPs*: the fact that infant RPs may occur in transient vs. persistent and single vs. multiple forms, raises the possibility that an impaired developmental trajectory of the DMN contributes to the developmental trajectory of infant RPs. During normal development, the functional connectivity of the DMN, particularly between its posterior and anterior hubs, increases significantly over time(70). Our finding that DMN iFC decrements between anterior and posterior parts are strongest in adults with multiple *and* persistent RPs may thus indicate a differential developmental DMN trajectory in those individuals.

(iii) *For potential interventions*: if DMN activity can be modulated by specifically targeted interventions, then these may be used to support individuals with infant RPs. For instance, Brauer and colleagues demonstrated, that the functioning of the DMN could be increased by

frequent maternal touch(71). Additionally, socially-induced emotion regulation enhances positive feelings by recruiting the target person's DMN(69). Beyond that, transcranial magnetic stimulation has been shown to be effective for boosting DMN activity(72). Such interventions may be particularly appropriate for individuals with multiple *and* persistent RPs as they have the highest risk for behavioral and emotional problems.

Strengths/limitations: (i) One particular strength of the present study is its prospective design from birth to adulthood, with multiple/persistent RPs assessed before adult behavioral and emotional problems started. Furthermore, access to diverse demographic, socio-economic and neonatal variables allowed us to match study groups with respect to gestational age, sex, SES or scanner distribution, limiting the risk of confounding variables to bias our results.

(ii) As can be seen from supplemental table S4, participants of the MRI subsample may represent a positive selection of the whole sample. However, this is not necessarily unique to the present MRI sample. It is well known that cognitively and mentally 'fitter' individuals are more likely to take part in the more demanding MRI scanning procedure than individuals suffering from mental health problems (e.g.(73, 74)). While not invalidating the results, the group differences in this cognitively and mentally "fitter" subsample may only represent the lower boundary of what could have been observed if more impaired participants were included.

(ii) Due to the study design, approximately 64% (68% in the MRI sub-sample) of the infants were born with neonatal risks (i.e. very preterm and/or with very low birth weight) and were thus at increased risk for potential developmental problems. However, by employing an additional control analysis using behavioral and MRI data from term born participants only (cf. Figure S2), we made sure that our results are generalizable to a population of individuals with multiple/persistent RPs but less neonatal risks.

(iii) A major drawback of our study is the lack of rs-fMRI data in infancy before RPs occurred. This may have enabled us to determine whether DMN/SN iFC alterations are the cause or

consequence of RPs. Future studies may investigate DMN/SN iFC in infants with and without RPs and track their development longitudinally.

(iv) The present study's focus was on potential biological mediators of long-term behavioral problems following infant RPs. Therefore, we did not consider further factors (e.g. genetic or environmental factors) which may have contributed to variance in adult behavior. For instance, several studies suggested that suboptimal parenting may have negative effects on neurodevelopmental outcome(75). Future studies may investigate the influence of other factors on the behavioral outcome of individuals with infant RPs in more detail.

Conclusion

Results demonstrate that adults with infant RPs have more avoidant personality traits that are mediated by the DMN.

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Disclosures

Conflict of Interest: None declared. All authors report no biomedical financial interests or potential conflicts of interest.

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Tables

Table 1. Demographic data of the whole sample and MRI sub-sample

	Whole sample			**MRI sub-sample**		
	Never RPs	Multiple/Persistent RPs		Never RPs	Multiple/Persistent RPs	
	n=259 (75.7%)	n=83 (24.3%)	*p-value*	n=71 (62.2%)	n=43 (37.8%)	*p-value*
Age: M (SD)	27.44 (1.81)	28.14 (1.85)	0.002	27.8 (1.96)	28.5 (1.87)	0.095
Sex: N (%)			0.71			0.77
Male	131 (50.6%)	40 (48.2%)		36 (50.7%)	23 (53.5%)	
Female	128 (49.4%)	43 (51.8%)		35 (49.3%)	20 (46.5%)	
Gestation (weeks): M (SD)	36.73 (4.17)	36.71 (4.39)	0.97	37.2 (3.78)	37.7 (3.47)	0.49
Birth weight (grams): M (SD)	2705 (960)	2611 (951)	0.44	2713 (919)	2765 (822)	0.76
Socioeconomic status: N (%)			0.83			0.24
High	81 (31.3%)	26 (31.3%)		25 (35.2%)	15 (34.9%)	
Middle	111 (42.9%)	33 (39.8%)		32 (45.1%)	14 (32.6%)	
Low	67 (25.9%)	24 (28.9%)		14 (19.7%)	14 (32.6%)	

Statistics: t-tests for interval scaled variables and chi-square tests for nominal variables.

Table 2. Whole sample: Adults with RPs have more behavioral and emotional problems than adults without infant RPs

	Never RPs	Multiple/Persistent RPs	Mann-Whitney-U-Test p-value
	n=254	n=79	
YASR			
Sum scales (T-score)			
Total problems	39.57 (8.85)	42.99 (8.84)	**.002***
Internalizing problems	45.34 (11.29)	49.44 (11.90)	**.005***
Externalizing problems	42.69 (8.14)	45.20 (7.54)	**.014**
DSM-oriented scales (T-score)			
Depressive	52.69 (5.41)	53.90 (6.13)	.071
Anxiety	51.38 (3.42)	51.67 (3.69)	.578
Somatic	53.04 (5.65)	54.11 (5.40)	**.010**
Avoidant personality	53.47 (6.17)	56.01 (6.92)	**<.001***
Attention deficit/hyperactivity problems	50.36 (0.83)	50.75 (1.61)	**.036**
Antisocial personality	51.12 (2.65)	51.73 (2.93)	**.011**

Data are represented as mean (Standard Deviation). *Significant after Bonferroni-adjustment: $p<0.006$

Figure Legends

Figure 1. Flow-diagram depicting the final sample compositions

Figure 2. RPs-related iFC differences in the DMN overlap with the social cognition network and are associated with avoidant personality traits.

A1. One-sample t-tests ($p<0,05$, FWE-corrected) of the DMN for adults with (bright green) and without infant RPs (blue). Dark green areas represent brain regions where one-sample t-tests for both groups overlap. Images are displayed according to the Neurological Convention.

B1. Adults with infant RPs demonstrate decreased iFC of the DMN in the precuneus and medial prefrontal cortex (yellow areas; $p < 0,05$, FWE-corrected). Red voxels mark the social cognition network ($p<0,05$, FWE-corrected) as identified in the meta-analysis of Schilbach and colleagues(31).

C1. The one-way ANCOVA within adults with infant RPs revealed a dose effect of RPs on DMN iFC. Scheffé's post-hoc t-tests revealed that adults with multiple *and* persistent RPs had a significantly lower iFC than adults with multiple but transient RPs. Barplots show mean residual DMN iFC for each group with 95%-confidence intervals.

D1. Within the RPs-group, decreased iFC of the DMN is significantly correlated with avoidant personality traits (Spearman's rank correlation: $r = – 0.42$, $p = 0.006$).

A2. Same logic as in A1 for the SN. B2. Between group differences in SN iFC (yellow areas; $p < 0,05$, FWE-corrected) show little overlap with the emotional processing network identified by Schilbach and colleagues (red areas; $p<0,05$, FWE-corrected). C2. The one-way ANCOVA within the RPs-group showed no significant dose effect of RPs on SN iFC. D2. SN iFC within the RPs-group shows no significant correlation with avoidant personality traits ($r = 0.12$, $p = 0.44$).

Figure 3. Decreased DMN iFC in the precuneus and medial prefrontal cortex mediates the association between infant RPs and avoidant personality traits.

Displayed are the total effect (c), direct effect (c') and indirect effect (a*b) for the triangular relationship of infant RPs ("group"), adult avoidant personality traits ("Avoidant") and residual DMN iFC.